REMARKS

Claims 1-5 and 8-18 are pending in this application. Claim 4 has been withdrawn from consideration as being drawn to a non-elected species.

Submitted herewith is a Declaration under 37 CFR § 1.132 by Dr. Naftali Primor. The Declaration evidences the non-obviousness of the presently claimed invention.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, claims 1-3, 5, and 8-18, have been rejected under 35 USC § 103(a) as being unpatentable over Politi et al. (US Patent 6,057,297).

Examiner Winston asserts that the Politi *et al.* product appears to be the same as the presently claimed product because the Politi *et al.* product is a non-toxic venom product that has pharmaceutical activity that relates to pain relief. The Examiner points to col. 4, lines 14-18; col. 3, lines 52-55; and Example 8; of the Politi *et al.* reference in support of his position. The Examiner asserts that while Politi *et al.* does not expressly teach the claimed purification method and administration, the selection of such parameters are a matter of "judicious selection and routine optimization" within the purview of the skilled artisan.

In view of the remarks set forth herein, this rejection is respectfully traversed.

A proper case of obviousness under 35 U.S.C. §103, requires that the prior art, as a whole, must suggest the desirability of making the claimed combination and provide a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

The *Dow* court further held that "In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." The court in *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994), held that "A prior art reference may be said to *teach away* when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." The court in *Busch & Lamb, Inc. v. Barnes-Hind/Hydro curve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986), held that "A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered."

Three requirements must be satisfied to establish a *prima facie* case of obviousness. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v.*

Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991). Lastly, the prior art reference must teach or suggest all the limitations of the claims. *In re Wilson,* 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Regarding motivation to modify a reference, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *See Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so. " *In re Mills,* 916 F.2d 680 at 682.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). In addition, if a proposed modification or combination of prior art references would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 813 (CCPA 1959).

It is submitted that a *prima facie* case of obviousness has not been established because the Politi *et al.* reference fails to teach or suggest all of the limitations of the claims as required by *In re Wilson.* Specifically, (i) Politi *et al.* does not teach or suggest a snake venom product; (ii) Politi *et al.* does not teach or suggest a substantially non-toxic snake venom isolate that has an analgesic effect; and (iii) Politi *et al.* does not teach or suggest a substantially non-toxic fraction isolated from snake venom having the characteristics of a fraction purified from said venom by Mono Q ion-

exchange chromatography where the isolate has an analgesic effect. In fact, Politi *et al. teach away* from a substantially non-toxic snake venom isolate that has an analgesic effect.

Present claim 1 recites a substantially non-toxic fraction isolated from snake venom having the characteristics of a fraction purified from said venom by Mono Q ion-exchange chromatography, wherein said fraction has an analgesic effect after a lag period, and wherein said snake is selected from the group of snake families consisting of Atractaspidae, Elapidae, Crotalidae, Hydrophidae and Viperidae, with the exception of Vipera Xanthina. Present claims 2-3, 5 and 8-13 are directly or indirectly dependent on independent claim 1.

Present claim 14 recites a method for isolating a substantially non-toxic fraction from snake venom, wherein said fraction has an analgesic effect, comprising applying whole venom to an ion exchange column and eluting the fraction with an aqueous buffer, wherein said snake is selected from the group of snake families consisting of Atractaspidae, Elapidae, Crotalidae, Hydrophidae and Viperidae, with the exception of Vipera Xanthina. Claims 15-18 are directly or indirectly dependent on independent claim 14. A brief analysis of Politi *et al.* is set forth below.

Politi *et al.* is directed to ***synthetic*** compounds that inhibit zinc-dependent metalloproteinases where the synthetic compounds are used to treat pathological conditions associated with activation of endogenous metalloproteinases in mammals. *See* Politi *et al.*, the abstract.

Politi *et al.* describe that the venom of snakes belonging to the family Crotalidae contain enzymes that are hemorrhagic factors. These hemorrhagic factors rapidly induce extensive internal hemorrhages in bite victims. The hemorrhagic factors comprise a large number of enzymes isolated from venom where the enzymes possess common properties including the way that zinc bonds to certain amino acids in a protein chain. *See* Politi *et al.*, the paragraph bridging cols. 1 and 2. These hemorrhagic enzymes are snake venom metalloproteinases. *See* Politi *et al.* at col. 1, lines 48-61 and col. 2, lines 1-6 and 28-31. Politi *et al.* describes that the invention provides synthetic compounds that have a powerful inhibitory activity on such snake venom metalloproteinases. *See* Politi *et al.* at col. 2, lines 41-45.

The Examiner supports his position that the Politi *et al.* product appears to be the same as the presently claimed product in that the Politi *et al.* product is allegedly a non-toxic venom product that has pharmaceutical activity that relates to pain relief, by pointing to Politi *et al.* at : (i) col. 4, lines 14-18; (ii) col. 3, lines 52-55; and (iii) Example 8. Each of the passages (i)-(iii) referenced by the Examiner, are addressed below.

Regarding (i), Politi *et al.*, at col. 4, lines 5-8, describes that small peptides isolated from snake venom "which probably" have the job of inhibiting metalloproteinases, have extremely specialized activity. Politi *et al.*, at col. 4, lines 10-17, asserts that his aim was to synthesize compounds "which are in some way similar to the peptides found in the venom, but which have a much higher inhibiting activity" (approximately 1000 times higher).

Accordingly, the product of Politi *et al.* is ***not*** a "non-toxic venom product that has pharmaceutical activity that relates to pain relief." Rather, the product of Politi *et al.* is a ***synthetic product that inhibits zinc-dependent metalloproteinases.*** In addition, the above passage of Politi *et al.* clearly conveys that the synthetic inhibitors of Politi *et al.* are advantageous over small peptides because the synthetic inhibitors exhibit approximately 1000 times the activity exhibited by small peptides.

Lastly, with regard to (i), nowhere is it suggested that snake venom isolates, either hemorrhagic enzymes (metalloproteinases) or small peptides, exhibit an analgesic effect. To the contrary, this passage ***teaches away*** from small peptides isolated from snake venom, because it teaches that such peptides exhibit much lower activity than the activity exhibited by the Politi *et al.* synthetic inhibitors. Specifically, the skilled artisan in view of Politi *et al.* would be led in a direction different than that taken by the present inventors, i.e., would be led away from investigating small peptides isolated from snake venom. *See In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994).

Regarding (ii), at col. 3, lines 52-55, Politi *et al.* describes that "The present invention...can be used for therapy in a large number of pathological situations, which situations range from snake bite poisoning to...." Thereafter, at lines 57-59, Politi *et al.* describes that the inventive compounds can be used for human therapy in "any pathological situation in which the predominant pathological agent is a zinc-dependent metalloproteinase." This passage conveys that zinc-dependent metalloproteinases are pathological agents.

Accordingly, with regard to (ii), Politi *et al.* does ***not*** describe that zinc-dependent metalloproteinases are non-toxic and exhibit an analgesic effect. In addition, Politi *et al.* describes at col. 3, lines 6-10, that "The present inventors have found that it is possible to develop a new method for antagonizing the lethal effects of certain classes of snake venom by using the inhibitors of the enzymes produced by snake venom."

Regarding (iii), in complete contrast to the Examiner's assertion, Example 8 describes that a number of ***toxic hemorrhagins,*** i.e., zinc-dependent metalloproteinases, were extracted from snake venom. *See* Example 8 at col. 16, lines 46-48. Thereafter, the synthetic inhibitors of Politi *et al.* were added to the isolated snake venom hemorrhagins and inhibitory activity of the synthetic compounds was determined. *See* Politi *et al.* at col. 17.

Accordingly, the isolated snake venom fraction described in Example 8 is ***not*** a substantially non-toxic snake venom fraction that has an analgesic effect. Rather, the isolated snake venom fraction is a ***pathological zinc-dependent metalloproteinase*** that causes hemorrhaging, i.e., a hemorrhagic enzyme.

In contrast to Politi *et al.,* the present claims recite a substantially non-toxic fraction isolated from snake venom that has an analgesic effect. The zinc-dependent metalloproteinase pathological agents described in Politi *et al.* can not be a non-toxic snake venom fraction that has an analgesic effect. In addition, the synthetic inhibitors described in Politi *et al.* can not be a non-toxic snake venom fraction that has an analgesic effect.

A. Declaration under 37 CFR § 1.132 evidencing non-obviousness.

In further support of the non-obviousness of the invention claimed in present claims 1-5 and 8-18, submitted herewith is a Declaration under 37 CFR § 1.132 by Dr. Naftali Primor. Dr. Naftali Primor is an inventor of the invention described and claimed in the instant application, and is a recognized expert in the field of snake venom.

Opinion testimony is entitled to consideration and some weight. *See In re Lindell*, 385 F.2d 453, 456 (CCPA 1967), which held that "some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him." The court in *In re Carroll*, 601 F.2d 1184 (CCPA 1979), held that an expert opinion on what the prior art taught, supported by documentary evidence and formulated, received considerable deference. Lastly, an affidavit of an applicant as to the advantages of his or her claimed invention cannot be disregarded for this reason alone. *See In re McKenna*, 203 F.2d 717 (CCPA 1953).

In the Declaration, Dr. Primor states that the Politi *et al.* Reference fails to describe a component isolated from snake venom that is non-toxic and has an analgesic effect after a lag period, and that in his expert opinion the Politi *et al.* reference not only fails to contain any description or suggestion that would lead an artisan to the presently claimed product and method of use, but in fact, contains a description that would lead the artisan away from the presently claimed product and method of use.

Regarding col. 4 of Politi *et al.*, it is Dr. Primor's expert opinion that the synthetic inhibitors described in the Politi *et al.* reference are significantly different from small

peptides isolated from snake venom because, as described in the Politi *et al.* reference, the inhibitors have "much higher" activity, i.e., 1000 times higher, than the activity exhibited by small peptides isolated from snake venom. Dr. Primor further states that nowhere is it suggested that such snake venom isolates exhibit analgesic activity. In addition, it is Dr. Primor's expert opinion that an investigator reading the Politi *et al.* reference would have no motivation to explore such small peptides isolated from snake venom.

Regarding Example 8 of Politi *et al.*, it is Dr. Primor states that this example describes isolating a number of toxic hemorrhagins, i.e., zinc-dependent metalloproteinases. Dr. Primor further states that Example 8 does not suggest or describe that the isolated hemorrhagins are non-toxic or have an analgesic effect.

With regard to col. 3 of Politi *et al.*, Dr. Primor states that the reference describes that zinc-dependent metalloproteinases are pathological agents. Dr. Primor states that the reference and does ***not*** describe that such metalloproteinases are non-toxic and exhibit an analgesic effect. Dr. Primor states that the zinc-dependent metalloproteinase pathological agent described in the Politi *et al.* reference ***cannot*** be a non-toxic snake venom fraction that has an analgesic effect.

Lastly, Dr. Primor states that the Politi *et al.* reference relates to synthetic inhibitors of zinc-dependent metalloproteinase pathological agents and not to a non-toxic fraction isolated from snake venom that has an analgesic effect as set forth in the instant application.

In view of the remarks set forth herein and the Declaration under 37 CFR § 1.132 by Dr. Primor, it is submitted that nothing in the Politi *et al.* reference renders claims 1-3, 5, and 8-18, obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be patentably distinguishable over Politi *et al.* Favorable action with an early allowance of all currently pending claims 1-3, 5, and 8-18, in this application is earnestly solicited. Moreover, when allowable subject matter is found herein the examiner is invited to reincorporate the non-selected species and claim 4 directed to a non-selected species.

The Examiner is welcomed to telephone the undersigned attorney if he has any questions or comments.

Respectfully submitted,
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